Chapter 12: Menopause and Disorders of Neurologic Function, Mental Health, and the Eye

Victor W. Henderson, M.D., M.S.; Barbara E. K. Klein, M.D., M.P.H.;† and Susan M. Resnick, Ph.D.‡*

Key Points[a]

1. Menopausal ERT appears to help preserve certain cognitive skills immediately after induced menopause [B] and during normal aging [C].
2. Estrogen therapy begun after menopause may reduce risk of Alzheimer's disease [C]. In contrast, limited data from RCTs indicate that estrogen alone begun after the onset of dementia does not seem to improve Alzheimer symptoms [B].
3. In observational studies, ERT does not modify stroke risk in older healthy women [C].
4. For many neurologic disorders (epilepsy, migraine, multiple sclerosis, and Parkinson's disease), observational study findings do not indicate an overall positive or negative impact of menopause or HRT on neurologic symptoms or disability [C]. Some sleep disturbances that occur during the climacteric may benefit from ERT [C].
5. Hormonal changes associated with menopause have shown little direct impact on mood [C]. Although clinical implications are uncertain, limited data suggest a beneficial effect of estrogen on mood [B].
6. There is little evidence that HRT alters risk for age-related maculopathy, cataract, or dry eye [C].
7. Few clinical characteristics or diagnostic procedures identify subgroups of women particularly likely to benefit from HRT for the prevention or treatment of disorders of neurologic function, mental health, or the eye [D]. Despite a strong biologic rationale, clinical data are sparse. Thus, recommendations regarding HRT to prevent or ameliorate those disorders are limited. Well-characterized benefits and risks of HRT for other organ systems override considerations of potential benefit for the brain and eye [D].

Menopausal ERT appears to help preserve certain cognitive skills immediately after induced menopause and during normal aging.

* From the Donald W. Reynolds Center on Aging, University of Arkansas for Medical Sciences, Little Rock, AK, U.S.A.

† From the University of Wisconsin-Madison, Ocular Epidemiology, Madison, WI, U.S.A.

‡ From the Cognition Section, Laboratory of Personality and Cognition, National Institute on Aging, NIH, Bethesda, MD, U.S.A.

[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgement. (See also table 12–1).

1. Introduction

Menopause is associated with sharp declines in concentrations of circulating estrogen and other alterations in the hormonal milieu.[1] The hormonal changes affect a variety of reproductive and nonreproductive tissues, including the CNS eye; HRT with estrogen or other sex steroids may influence brain and eye functions (table 12–1).[2]

Limited data suggest a beneficial effect of estrogen on mood.

In the brain and eye,[3,4] as in other target organ systems, estrogen interacts with specific intranuclear receptors to regulate protein synthesis. Within the CNS system, individual neurons can express ERα, the ERβ, neither receptor, or occasionally both receptor types. (See ch. 5.)[3] Androgen and PRs are found in populations of neurons. Within the brain, some estrogen actions occur within a matter of seconds or minutes, too rapidly to involve genomic activation. Those rapid estrogen effects are believed to involve receptors located in the cell membrane.[5] Finally, estrogen can influence brain and eye functions indirectly, through effects on nonneural and nonocular tissues, including the vasculature and the immune system.

Despite a strong biologic rationale, there is no strong evidence based on consistent findings from well-designed RCTs, controlled trials regarding the clinical importance of HRT for the central nervous system and the eye. Relevant preclinical and clinical data are beginning to emerge for several disorders. In some areas, a developing consensus may help guide clinical decisions on prevention and treatment.

Age-associated cognitive decline is considered in this chapter, as are dementia, stroke, epilepsy, migraine, multiple sclerosis, Parkinson's disease, and sleep disorders. With regard to mental health, there are data on mood and schizophrenia. Eye disorders of interest include age-related maculopathy, cataract, and dry eye.

2. Age-Associated Cognitive Decline and Neurologic Disorders

Clinical data exist for age-associated cognitive decline in healthy women and for a number of neurologic conditions. Some topics have been reviewed.[6]

2.1 Age-Associated Cognitive Decline

Memory and other cognitive abilities change over time during adult life. Changes that represent usual or normal accompaniments of aging are not viewed as pathologic. Modest cognitive decrements initially detectable in middle age are accentuated at elderly age. In general, cognitive tasks that depend on previously learned knowledge are more resistant to decline than tasks involving new information or requiring the manipulation of old information.

2.1.1 Effects of Estrogen

Considerable data indicate that sex hormones measurably influence brain functioning throughout life. Higher cognitive scores in childhood are associated with a later age at menopause.[7] There is little evidence that menopause per se initiates cognitive deterioration.

As inferred from in vitro and animal studies, estrogen has the potential to modulate cognitive processes.[6] Within the brain, estrogen affects a number of neurotransmitter systems, including cholinergic, noradrenergic, serotoninergic, and dopaminergic pathways,[6] which are involved in aspects of memory and attention. In ovariectomized rodents, estrogen improves memory performance on a variety of behavioral tasks.[8–10] Estrogen interacts with NGF and other neurotrophins,[11] promotes the growth of nerve processes,[12,13] and enhances synaptic plasticity.[14] Estrogen protects neurons from a variety of endogenous and exogenous insults.[15,16] In animal studies, estrogen augments glucose transport into the brain and increases cerebral metabolism.[17,18]

In human studies, estrogen influences the pattern of brain activation during the performance of cog-

TABLE 12–1

Estrogen Actions Potentially Germane to Disorders of the Brain and Eye*

Effects on neurotransmitter systems
Acetylcholine Noradrenaline Serotonin Dopamine Others
Neurotrophic actions
Interactions with neurotrophins Neurite extension Synapse formation and synaptic plasticity
Protective actions
Augmentation of blood flow Enhancement of glucose transport into the brain Protection against apoptosis Antioxidant properties Anti-inflammatory properties
Effects on proteins involved in Alzheimer's disease
Apolipoprotein E Amyloid precursor protein
Effects on ocular tissues
Effects on light transmission through the crystalline lens

* Modified from Henderson VW, 1997.[2]

nitive tasks, as inferred from measures of cerebral blood flow.[19–21] Chronic estrogen use is associated with greater increases in relative blood flow in regions of the temporal lobe.[22] As described below, effects of estrogen on cognitive abilities of healthy adult women have been studied in various clinical settings; the findings have been inconsistent but often positive.

Primary prevention: The possibility that estrogen might help preserve cognitive function during normal aging has been examined in observational studies.[23] Serum estrogen concentration in postmenopausal women does not appear to be closely related to cognitive skills,[24] although one study reported a positive relationship between levels of bioavailable estradiol and verbal memory but an

inverse relation with nonverbal memory.[25] Healthy, community-dwelling older women who use ERT, with or without a progestin, appear to perform better on cognitive tasks.[26,27] In one well-characterized, longitudinally assessed American cohort, postmenopausal women receiving estrogen performed significantly better on measures of nonverbal and verbal learning and memory than menopausal women who had never used estrogen.[28,29] In other American cohorts estrogen users scored better on specific tests of verbal memory, naming, and abstract reasoning[30] or on cognitive screening tasks.[31,32] In Austria, a population-based study found that postmenopausal women currently using estrogen performed better than nonusers on several psychometric measures; the greatest differences were seen in complex problem-solving tasks and psychomotor speed.[33] In a Dutch patient registry, women receiving HRT performed significantly better on a composite measure of psychomotor speed but did not differ significantly from nonusers on measures of memory or cognitive flexibility.[34] Analyses in two large American cohorts, did not show appreciable differences in a variety of cognitive measures between users and nonusers of postmenopausal estrogen.[35,36] Longitudinal observations imply that estrogen may help preserve cognitive[30] or functional[37] abilities, although current estrogen use failed to protect against cognitive decline on a brief psychometric instrument in another observational study.[31]

Healthy, community-dwelling older women who use ERT, with or without a progestin, appear to perform better on cognitive tasks.

Treatment of symptoms: Several randomized, controlled clinical trials have examined cognitive effects of estrogen after natural or surgical menopause. Treatment was up to 3 months in duration. Women given estrogen outperformed women given placebo on a variety of psychometric measures.[38,39] On long-term memory tasks, improvement was more apparent when verbal, as opposed to nonverbal, memory was assessed.[38–40] Verbal memory enhancement was also described in a placebo-controlled study of younger women whose ovarian function had been suppressed with a GnRH agonist before "add-back" treatment with estrogen.[41] Positive findings generally occurred in acute studies of relatively younger women after ovarian function was abruptly suppressed;[38,39,41] few clinical trials considered ERT initiated at a later point after natural menopause. In contrast to these generally positive findings, a randomized, placebo-controlled trial of estrogen in 62 women who had previously undergone hysterectomy, conducted by Finnish investigators, detected no benefit of estrogen on measures of psychomotor speed, attention, working memory, or visual memory.[42]

2.1.2 Recommendations for Age-Associated Cognitive Decline

Recommendations for the primary prevention of age-associated cognitive decline and for the improvement of cognitive skills in otherwise healthy women are derived primarily from inconsistent findings of observational studies and uncontrolled trials and from a limited number of short-term RCTs. In observational studies, women who choose to use estrogen differ in a number of ways from women who do not,[43] and positive findings in such studies may reflect unrecognized bias or confounding.[44] Evidence that estrogen use after menopause is associated with better cognitive skills remains weak. The evidence is somewhat better in short-term studies of younger women with induced menopause. On the basis of available information, the desire to protect against age-associated cognitive decline should not generally affect decisions about whether to use ERT, except possibly in women undergoing surgical menopause.

2.2 Dementia

Dementia represents a decline in memory and other cognitive abilities severe enough to have a deleterious effect on daily function. In many regions, Alzheimer's disease is the commonest

cause of dementia;[45] whether its occurrence or progression is affected by estrogen has been of research interest. Very few data directly address whether estrogen might influence dementia due to disorders other than Alzheimer's disease.

2.2.1 Alzheimer's Disease

As an age-associated disorder, Alzheimer's disease rarely appears before menopause, but its prevalence increases exponentially between the 6th and 10th decades of life.[46] During the first half of the 21st century, it is expected that current trends of an increasing proportion of elderly people in the population will continue for both developed and developing countries, and that the burden of Alzheimer's disease will expand accordingly. Alzheimer's disease is 1.5 to 3 times more common among women than men,[46] in part because of sex differences in longevity.

Alzheimer's disease is a progressive neurodegenerative disorder characterized by the insidious onset of memory loss and other cognitive symptoms that relentlessly worsen over a period of years. Pathologic features include intracellular neurofibrillary tangles and extracellular neuritic plaques. The latter are associated with inflammatory proteins and typically contain a central core composed of β-amyloid. There is evidence that oxidative damage contributes to Alzheimer pathology.

Both genetic and nongenetic factors are implicated in Alzheimer pathogenesis. Autosomal dominant mutations are important causes of early-onset, but not late-onset, illness. For the common, late-onset form of Alzheimer's disease, several genes may modify susceptibility. The best-recognized susceptibility gene encodes the lipid transport protein apolipoprotein E, which is involved in neuronal repair processes. Increased Alzheimer susceptibility is conferred by the apolipoprotein E ε4 allele,[47] which is associated with reduced neuronal sprouting compared with the more common ε3 allele.[48] Sex appears to modify risk: the ε4 allele increases risk more for women than men.[49,50]

Of theoretical benefit in Alzheimer's disease are neurotrophic and neuroprotective effects of estrogen, as well as effects on cholinergic and other neurotransmitter systems. In the laboratory, protective effects against programmed neuronal death (apoptosis),[51] inflammation,[52] and oxidative damage[15,16] appear particularly relevant to Alzheimer pathogenesis. Finally, estrogen increases the expression of apolipoprotein E within select brain regions[53] and inhibits the formation of β-amyloid from its precursor protein.[54] For these reasons, investigators have inquired whether ERT might have roles in preventing or treating Alzheimer's disease.

Very few data directly address whether estrogen might influence dementia due to disorders other than Alzheimer's disease.

Primary Prevention: In the early 1990s, cross-sectional analyses compared current estrogen use in women with Alzheimer's disease and women in the same age group without dementia.[55–57] Although subject to important bias, results implied that ERT may reduce Alzheimer risk. Several earlier case-control studies had failed to document a link between estrogen use and Alzheimer risk, but since 1994 nine additional studies have assessed the relation between ERT and Alzheimer's disease.[57–66] Most analyses were based on data for estrogen use collected prior to the onset of dementia symptoms,[56–61,63,64] and most, but not all,[59] found an association between the use of estrogen after menopause and protection against Alzheimer's disease. In these case-control and cohort studies, estimates of total reduction in RR are about 50 percent.[60] Estrogen effects were reported for women with and without the ε4 allele of apolipoprotein E.[61]

If ERT reduces Alzheimer risk, it might be expected that greater estrogen exposure would be associated with greater risk reduction. Several studies of estrogen exposure assessed by dosage or duration of use support that contention. In the Leisure World Study, risk estimates for Alzheimer's dis-

ease decreased significantly with increasing dose of the longest used oral estrogen preparation.[60] Significant associations between the duration of estrogen use and the degree of risk reduction were found in analyses from Leisure World,[60] New York City,[61] and Rochester, MN.[66] However, in a longitudinally followed cohort in Baltimore, MD, there was no significant link between duration of use and the magnitude of risk reduction.[63] No data address whether there may be a critical period during which ERT exerts its putative beneficial effects (e.g., the early menopausal period versus the senium). There are no clinical studies on possible beneficial or deleterious effects of dietary estrogens on Alzheimer risk in women, although one study reported a link between higher midlife consumption of tofu, a rich source of isoflavone phytoestrogens, and poor cognitive test performance in men.[67]

Treatment of Symptoms: Cholinergic systems of the brain are markedly impaired by pathologic changes of Alzheimer's disease, and medications that increase cholinergic activity by inhibiting the breakdown of acetylcholine are of modest benefit.[68–70] Antioxidants may slow disease progression (e.g., vitamin E)[71] or modestly improve symptoms (e.g., gingko biloba).[72] In observational studies of women with Alzheimer's disease, HRT is associated with milder cognitive deficits,[73,74] although most estrogen use is of long-standing duration. Results from relatively short-term randomized clinical trials of estrogen use are less supportive. Positive results in a 3-week study of conjugated estrogens in 14 women with Alzheimer's disease[75] and suggestive results in an 8-week study of transdermal estradiol in 12 women[76] are offset by decidedly negative findings in two larger trials of conjugated estrogens. One randomized trial in 42 menopausal women with mild to moderate Alzheimer's dementia showed no difference between the estrogen and the placebo group after 16 weeks on the primary cognitive outcome measure or on secondary measures of global change and functional status.[77] Women with mild to moderate Alzheimer symptoms who had undergone hysterectomy were randomized in a second trial to one of two treatment arms using different estrogen dosages (N = 42 and 39) or to placebo (N = 39). At 12 months, there was no benefit of estrogen on measures of global change, cognition, or function.[78] Preliminary observational analysis of concomitant estrogen use in a large, multicenter trial of tacrine raises the possibility that estrogen given in combination with a cholinergic drug may be useful; greatest improvement was observed in the subgroup taking ERT at the time of initial randomization to tacrine.[79]

Results implied that ERT may reduce Alzheimer risk.

2.2.2 Vascular Dementia

Another common cause of dementia is ischemic vascular disease of the brain, particularly multiple strokes, that is, multi-infarct dementia.[45] In some Asian countries, the prevalence of vascular dementia may exceed that of Alzheimer's disease.[80] Symptoms of multi-infarct dementia often begin abruptly, and cognitive decline may occur in a stepwise manner. Neurologic examination typically finds signs of focal brain damage, and radiologic studies, such as MRI usually confirm cerebral infarction. Neuroprotective effects of estrogen could be important. In experimental models of acute cerebral ischemia, estrogen reduces ischemic damage.[81–83] In one observational study, women with vascular dementia were less likely than healthy women to use HRT.[57] Stroke incidence, however, is not closely associated with the use of HRT (see below), and there is no defined role for menopausal estrogen in women with vascular dementia.

2.2.3 Recommendations for Dementia

Evidence from an increasing number of case-control and cohort studies provides substantial—but not compelling—evidence that use of estrogen after menopause reduces women's risk for Alzheimer's disease. A woman at high risk for

Alzheimer's disease from, for example, genetic predisposition or a strong family history in first-degree relatives, may wish to consider ERT if other potential benefits of treatment are not exceeded by well-recognized potential risks. Decisions concerning estrogen dosage, timing, and treatment duration should be guided by other medical considerations; the literature on Alzheimer's disease allows no consistent guidance. On the basis of data from a small number of RCTs,[77,78] estrogen monotherapy is not useful for the treatment of dementia in women diagnosed with Alzheimer's disease. Short-term side effects, including venous thrombosis,[75] breast tenderness, and withdrawal bleeding, are particularly worrisome in that population. Few data address estrogen effects in forms of dementia other than Alzheimer's disease.

2.3 Other Neurologic Disorders

2.3.1 Stroke

Stroke refers to brain disease caused by ischemic or hemorrhagic abnormalities in the vascular supply to the brain. (See ch. 8, sec. 7.) The incidence of stroke varies widely from country to country.[84] Its incidence rises dramatically with age, and worldwide, stroke is the second leading cause of death.[85] In the Framingham Study in the United States, rates for ischemic stroke are lower in women than men.[84] Atherosclerosis in arteries that supply blood to the brain predisposes to cerebral infarction.[86] Estrogen may reduce these atherosclerotic changes, perhaps due to favorable effects on the serum lipid profile and vascular endothelial function. (See ch. 8, sec. 3.2 and sec. 4.1.1).[87,88] Estrogen increases cerebral blood flow in humans.[89] In rats, estrogen reduces the extent of brain damage caused by acute infarction.[81–83]

In a number of observational studies, HRT is associated with reductions in risk for stroke death of 20–60 percent.[90] However, even in analyses restricted to ischemic stroke, HRT does not appear to reduce stroke incidence.[91,92] This conclusion is supported by secondary analyses in a large clinical trial among postmenopausal women with CHD; after a mean followup of 4 years, HRT had no effect on stroke risk.[93]

Among relatively younger women in the Nurses' Health Study, current hormone use was associated with higher risk of ischemic stroke.[91] There is good evidence that treatment of hypertension, the use of statins after MI, and carotid endarterectomy in patients with severe stenosis can reduce the risk of a first ischemic stroke due to atherothrombotic disease.[94] Because ERT may increase short-term cardiovascular risk,[93] there is a need for caution in beginning estrogen after recent ischemic stroke.

Stroke incidence, however, is not closely associated with the use of HRT.

2.3.2 Epilepsy

Epilepsy is a CNS disorder characterized by recurrent seizures. Epilepsy often begins in early life but can start at any age. Causes are legion. In rats, estrogen increases the excitability of hippocampal neurons[95] and exacerbates epilepsy by lowering the seizure threshold;[96] epileptogenic effects may be opposed by progesterone.[96] In women with so-called catamenial epilepsy, seizures tend to recur immediately preceding or during menstruation and are thought to be triggered by fluctuations in concentrations of ovarian hormones.[97] Catamenial seizures can occur during other phases of the menstrual cycle as well.[98] The use of estrogen-containing OCs does not increase seizure frequency.[99] Effects of menopause on epilepsy have not been well studied. Based on limited questionnaire data, epileptic women probably would not experience a change in seizure frequency or severity with menopause, but HRT may increase seizure frequency.[100,101]

2.3.3 Migraine

Migraine is a common disorder characterized by recurrent attacks of throbbing headache. Pain is often unilateral and is sometimes preceded by focal neurologic symptoms and accompanied by gastrointestinal symptoms. A questionnaire study

of households selected to be representative of the U.S. population found migraine prevalence to be greatest between ages 35 and 45 years and women to be affected three times as often as men.[102] Headache frequency is influenced by the menstrual cycle and pregnancy. Migraine attacks occur less often during middle age and beyond.[102,103] Menopause per se has been reported to have either little effect[104] or a beneficial effect[105] on migraine frequency. For women undergoing surgical menopause, migraine symptoms may worsen, and occasionally migraine first appears after menopause.[105] Effects of ERT on migraine have not been extensively studied, but estrogen treatment may reduce headache frequency.[106]

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2.3.4 Multiple Sclerosis

Multiple sclerosis, a chronic immunologic disorder of the CNS system, affects women more often than men. Disease incidence is greater among whites and with increasing latitude in temperate regions of the northern and southern hemisphere.[107] Pathologic changes of multiple sclerosis are mediated by T-cell lymphocytes directed against white matter antigens. Neurologic symptoms, which often first appear in early adulthood, depend on the focal distribution of pathologic changes. Exacerbations and remissions are common.

Estrogen influences cell-mediated immunity,[108] but the clinical relevance of estrogen to multiple sclerosis is not well established. Incidence is not increased by the use of OC medications.[109] Among women with multiple sclerosis, pregnancy does not increase long-term disability,[110] even though neurologic relapse often occurs during the postpartum period.[111] Some women experience a worsening of neurologic symptoms immediately prior to or during menstruation.[112,113] Effects of menopause or HRT on the neurologic symptoms or long-term course of multiple sclerosis are unknown.[114]

2.3.5 Parkinson's Disease

Parkinson's disease is a common, progressive neurodegenerative disorder of the basal ganglia. Symptoms include tremor, rigidity, and reduced movement (bradykinesia). Catecholamine neurotransmitters are characteristically reduced in Parkinson's disease, and most symptoms are attributed to the prominent loss of dopamine-containing neurons in the substantia nigra. Although the substantia nigra does not appear to contain large numbers of ERs in the adult brain,[115] estrogen affects dopamine receptors, the activity of dopaminergic neurons, and motor behaviors mediated by dopamine.[116–118]

There are a few studies of ERT and Parkinson's disease. For postmenopausal women with early Parkinson's disease, a retrospective chart review found estrogen use to be associated with milder Parkinsonian symptoms,[119] and results of a small crossover trial suggested that estrogen may enhance the response to dopaminergic therapy.[120] An American cohort study that compared women with idiopathic Parkinson's disease and women without stroke or dementia found no association between ERT and a Parkinson diagnosis.[121] For women in the cohort who had dementia as well as Parkinson's disease, estrogen use was linked to a significantly reduced likelihood of dual symptoms.

2.3.6 Sleep Disorders

A common symptom of the climacteric is the hot flush, characterized by an increase in core body temperature followed by cutaneous vasodilation, diaphoresis, tachycardia, and the transient sensation of heat. Troubled sleeping can be caused by hot flushes. Thermoregulatory disturbances in part reflect increased noradrenergic activity,[122] probably at the level of the hypothalamus, which in turn may be modulated by sex steroids. (See ch. 3, sec. 4.) Data from observational studies suggest that menopause is associated with increased sleep disturbances.[123,124] Nocturnal hot flushes are known to disrupt normal sleep patterns;[125,126] sleep disruption

is alleviated by estrogen treatment.[123,127] In a small pilot study, ERT ameliorated sleep apnea syndrome in menopausal women.[128]

2.3.7 Recommendations for Other Neurologic Disorders

Data from observational studies suggest that ERT does not protect healthy women from the occurrence of stroke. For epilepsy, migraine, multiple sclerosis, and Parkinson's disease, no compelling data indicate that ERT after menopause has substantial effects. Sleep disturbances, particularly during the climacteric and particularly when associated with hot flushes, may improve with ERT, although evidence from RCTs is lacking.

3. Disorders of Mental Health

3.1 Mood

Women of all ages have higher rates of depression than men.[129,130] Geriatric depression is an important public health concern.[131] Hot flushes and other menopausal symptoms may affect the quality of a woman's life.[132] The menopausal transition does not appear to represent a time of heightened vulnerability to affective disorders.[133]

A number of antidepressant drugs increase CNS levels of noradrenaline and serotonin, suggesting the importance of monoaminergic neurotransmitter systems in regulating mood. Estrogen influences noradrenalin and serotonin. Research findings on women with premenstrual dysphoric disorder or with major depression beginning in the postpartum period point toward the importance of sex hormones. Several short-term studies indicate that ERT given during the perimenopausal or menopausal period can diminish anxiety or enhance mood and subjective sense of well-being.[134–136]

Limited data suggest that severe depression in certain clinical populations is occasionally improved by ERT. Recent clinical experimental studies of postpartum depression indicate that reproductive hormones can be involved in the development of the disorder[137] and that estrogen can be effective in a major depressive episode with postpartum onset.[138] For women with a major depressive disorder, an older randomized, placebo-controlled trial of high-dosage estrogen showed significant amelioration of affective symptoms.[139] Among women with major depression treated with a selective SSRI, retrospective analyses do not strongly suggest important additive effects of concomitant ERT.[140,141]

Older postmenopausal women who use estrogen typically report fewer depressive symptoms than nonusers.[142] In RCTs in postmenopausal women without a diagnosis of depression, ERT has been reported to reduce scores on measures of depressive symptoms[134–136] and to have no effect on mood.[42,43] Apparent beneficial effects of estrogen on mood may be diminished by the concomitant administration of a progestin.[143]

Data from observational studies suggest that menopause is associated with increased sleep disturbances.

3.2 Schizophrenia

Schizophrenia is a chronic psychotic disorder characterized by delusions, auditory hallucinations, disorganized thought processes, affective blunting, and difficulty in sustaining goal-directed activity. Frequency does not significantly vary according to sex. Symptoms typically appear in the third decade of life, but onset occurs on average 3–5 years later for women than men.[144,145] Late-onset schizophrenia is more common in women,[146] although menopause does not appear to heighten risk.[145] Estrogen effects on dopaminergic or serotonergic systems of the brain could influence schizophrenic symptoms. Among ovulating women, a higher serum estrogen concentration has been associated with milder psychopathology.[147] In a small, open-label trial in women with schizophrenia, estrogen added to

standard antipsychotic drugs increased the speed with which psychotic symptoms improved, although the difference was not sustained.[148]

3.3 Recommendations for Mood Disorders and Schizophrenia

Women of all ages have higher rates of depression than men.

Possible estrogen effects on schizophrenia are inadequately addressed in the literature, and estrogen should probably not be considered as treatment for a major depressive episode or schizophrenia. There are weak data that estrogen might be considered for mild depressive symptoms attributed to hot flushes, sleep disturbances, or other climacteric symptoms. No data exist whether estrogen could be used as adjunct therapy for other depressive disorders during the menopausal transition or postmenopausal period.

4. Disorders of the Eye

Increasing age is often accompanied by visual loss or blindness, and among older people diminished visual acuity affects women more often than men.[149] Two of the most important causes of visual loss in older adults are age-related maculopathy and cataract. Another common problem among older adults is dry eye syndrome; symptoms, while usually not disabling, can be distressing and difficult to eradicate.

Because clinical data on estrogen and eye disorders are limited, visual considerations should not influence practice decisions on the use of HRT.

4.1 Age-Related Maculopathy

Maculopathy, which is most severely manifest as macular degeneration, is characterized by atrophy and neovascularization of the central portion of the retina. Age-related maculopathy affects women somewhat more often than men.[150] Although pathophysiologic mechanisms for the condition are unknown, several studies have evaluated possible effects of reproductive events and exogenous hormone use.

A case-control study from Rotterdam found that women with early surgical menopause were more likely to have macular degeneration than those with late surgical menopause.[151] Early spontaneous menopause was not associated with increased risk. In a cohort from the Blue Mountains region of Australia, increasing years from menarche to menopause, a measure of endogenous estrogen exposure, was associated with reduced odds of early changes of age-related maculopathy.[150]

In a U.S. multicenter case-control study, the use of HRT was associated with decreased risk for neovascular age-related macular degeneration,[152] the form of macular degeneration most commonly associated with severe visual loss. In a population-based cohort in Beaver Dam, WI, there was an inverse relation of borderline significance between the number of years of ERT and maculopathy, although there was no association between ever-use of estrogen and occurrence of maculopathy.[153] Analysis of pooled data from Rotterdam, Blue Mountains, and Beaver Dam failed to confirm an association between the use of menopausal estrogen and age-related maculopathy.[150] Similarly, the U.S. NHANES III found that current, but not past, use of HRT is associated with a lower prevalence of age-related maculopathy.[154] In an analysis of data from the Beaver Dam Eye Study, there was no evidence of a relationship between HRT and 5-year incidence of age-related maculopathy.[155]

Symptoms of dry eye improved significantly in an RCT of estrogen eye drops in postmenopausal women.

Maculopathy is among the most serious of the eye disorders, but evidence of estrogen benefit remains tenuous. No data address effects of HRT once maculopathy is evident.

4.2 Cataract

Cataract refers to a loss of transparency within the crystalline lens of the eye, which interferes with the transmission of light to the retina. The generic term encompasses different kinds of opacity, including opacities located in the nuclear, cortical, and posterior subcapsular portions of the lens. About 50 percent of the world's blind have cataract. Epidemiologic studies from Australia,[156] Asia,[157] Europe,[158] and North America[159–161] indicate that cataract affects elderly women more often than elderly men. In studies that discriminated among types of cataract, female sex was positively associated with both nuclear[156,161] and cortical[160,161] cataracts.

The relation of cataract formation to menopause or estrogen use has been considered in several observational epidemiologic studies. Early menopause was associated with cataract formation in reports from Beaver Dam and the Nato area of Japan[162,163] but not in a report from Blue Mountains.[164] In Beaver Dam, cortical cataract was more prevalent among older women; premenopausal women in the sixth decade of life had fewer nuclear cataracts than perimenopausal or postmenopausal women of the same age.[162] Transmission of light through the crystalline lens was greater in postmenopausal women receiving ERT than in women not taking estrogen or in men of similar age. The prevalence of cortical cataract was reduced among current estrogen users in the Blue Mountains Eye Study,[164 165] as was the severity of nuclear sclerosis in the Beaver Dam Eye Study.[162] Neither study, however, found an association between cataract and ever-use of menopausal hormones.[162,164] In the Blue Mountains data, but not Beaver Dam, posterior subcapsular opacity was more prevalent among older subjects who were current users of estrogen-progestin replacement therapy.[162,164] In the Beaver Dam Eye Study, there was no evidence of a relationship between HRT and the 5-year incidence of any type of age-related cataract.[155]

Estrogen effect on cataract has not been studied in randomized controlled studies.

4.3 Dry Eye

Dry eye, or keratoconjunctivitis sicca, is a common complaint among older adults.[166–168] Symptoms localized to the ocular surface include irritability, burning, itching, and sensations of dryness or the presence of a foreign body. Visual disturbances can occur, and severe manifestations occasionally threaten vision. Dry eye syndrome is pathogenetically heterogeneous and is caused by both decreased tear production and increased evaporative loss of the aqueous component of tears. Dry eye is associated with Sjögren's syndrome and other autoimmune diseases but frequently occurs in the absence of associated systemic illnesses.

Because clinical data on estrogen and eye disorders are limited, visual considerations should not influence practice decisions on the use of HRT.

Little evidence links estrogen to dry eye. Women are more likely to report symptoms of dry eye than men;[167–169] not all studies support the finding.[166] In the Beaver Dam Eye Study, the age-adjusted prevalence was 11 percent in men and 17 percent in women.[169] Menstrual status, history of hysterectomy, and use of HRT were not associated with dry eye.[169]

Gonadal steroids are important in the production of different tear components. Androgens may be the most important in the process.[170–172] It is hypothesized that the decline in androgen production after menopause, rather than the menopausal loss of estrogen, contributes to dry eye symptoms in older women.[170] Symptoms of dry eye improved significantly in an RCT of estrogen eye drops in postmenopausal women.[173] Clarification of the roles of hormones and of potential treatment possibilities awaits further investigation.

5. Future Needs

- Explore the possibility that SERMs may act as estrogen antagonists in the brain or eye.
- Evaluate in long-term RCTs the potential effects of HRT on age-associated cognitive decline.
- Evaluate in long-term RCTs the potential effects of HRT on primary prevention of Alzheimer's disease and vascular dementia.
- Evaluate the effectiveness of combination therapy with estrogen plus a cholinomimetic drug in RCTs for women with Alzheimer symptoms.
- Evaluate in RCTs the potential effects of HRT on primary prevention of Parkinson's disease and on symptoms of Parkinson's disease.
- Determine in RCTs whether estrogen combined with antidepressants or antipsychotic drugs might enhance the effects of these medications in depressive disorders and schizophrenia, respectively.
- Determine in long-term RCTs whether HRT might reduce incidence of age-associated maculopathy, cataract, or dry eye.
- If estrogen proves beneficial for disorders of neurologic function, mental health, or eye, the timing of therapy and the duration of usage for optimal benefit have to be resolved.
- If estrogen proves beneficial for disorders of neurologic function, mental health, or eye, the possibility that benefit may be altered by a progestin has to be resolved.

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Chapter 13: Best Clinical Practices: A Comprehensive Approach

Elizabeth Barrett-Connor, M.D.; Susan Hendrix, D.O.;† Bruce Ettinger, M.D.‡*

Nanette K. Wenger, M.D. Chair; Rodolfo Paoletti, M.D., Cochair; Claude J. M. Lenfant, M.D., Cochair; Vivian W. Pinn, M.D., Cochair

Panel: *Martin H. Birkhäuser, M.D.; Louise A. Brinton, Ph.D.; Aila Collins, Ph.D.; Peter Collins, M.D.; Pier Giorgio Crosignani, M.D.; Lorraine Dennerstein, A.O., M.B.B.S., Ph.D., D.P.M., F.R.A.N.Z.C.P.; Jan-Åke Gustafsson, M.D., Ph.D.; Victor W. Henderson, M.D., M.S.; Carlo La Vecchia, M.D.; Robert Lindsay, Ph.D.; Adriana Maggi, Ph.D.; Joan A. McGowan, Ph.D.; Anne McTiernan, M.D., Ph.D.; Maryann Redford, D.D.S., M.P.H.; Susan M. Resnick, Ph.D.; Jacques E. Rossouw, M.D.; Sherry Sherman, Ph.D.*

1. Introduction

The proportion of women living past the age of menopause has tripled during the past century, and is expected to increase steadily in the foreseeable future. If adulthood is defined as beginning at age 21, the average age at menopause as age 51, and the average life expectancy as age 81, women in the United States, in Europe, and in much of the developed world will live one-half their adult lives in the years after menopause, a time of relative estrogen deficiency compared to their reproductive years.

In recent years, the aging of the female population, together with the availability of "replacement" hormones, led to numerous studies of the menopause. Most of these studies were of middle-class white women living in the United States and Western Europe, with results that may not be relevant to other women. In addition, many studies were clinical or epidemiological observations of associations—less satisfactory for evidence-based medicine than randomized, placebo-controlled, double-blind clinical trials. Results from recent clinical trials studying the benefits of HRT have differed from observational studies. Results from additional large clinical trials, expected in the next 5 years, may further change thinking about the optimal management for the menopausal woman.

The menopause offers the health care provider an opportunity to assess each woman's health, her concerns, and the need for health promotion and disease prevention measures. Today's health care provider has to consider a bewildering array of changing "facts" and sees increasingly informed

* From the Division of Epidemiology, Department of Family and Preventive Medicine, UCSD School of Medicine, La Jolla, CA, U.S.A.

† From the Division of Gynecology, Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Hutzel Hospital, Detroit, MI, U.S.A.

‡ From the Division of Research, Kaiser Permanente Medical Care Program, Oakland, CA, U.S.A.

patients with strong personal convictions about the menopause and their need for medication. The provider must be prepared to discuss a variety of menopause or age-related topics, and decide what to recommend for a specific woman—often in less time than ever before.

The menopause offers the health care provider an opportunity to assess each woman's health, her concerns, and the need for health promotion and disease prevention measures.

Recommendations should be specific to each woman and her background. There are country-specific and cultural variations in menopause symptoms, the frequency of different postmenopausal diseases, clinical practice, health care resources, and affordable interventions. Country- and culture-specific practice will therefore vary, and appropriately so.

Recent research findings include:

- Increasing recognition of the need to address health promotion beyond the perimenopausal years, and in women with and without menopausal symptoms.
- The risks and benefits of lifestyle, pharmacological, and surgical interventions may change as women age.
- The tailoring of menopausal treatment to the individual woman should be based on her individual clinical profile and concerns.
- For the treatment of the climacteric syndrome, HRT remains the most effective pharmacologic intervention.
- The long-term benefits and risks of HRT continue to be assessed.
- HRT for long-term health promotion, as for osteoporosis, usually requires its continued use.
- New nonhormone therapies offer more options for prevention of common menopausal conditions, to be tested fully in clinical trials.
- Preventive drug therapy can start many years after menopause, particularly with respect to osteoporosis. This, however, may not be optimal.
- The risk for many disease outcomes can be reduced even in old age.

Research results are teaching us to be cautious before assuming that current practice is best. For example, although HRT remains the gold standard for the treatment of vasomotor and urogenital symptoms, as well as for the prevention of bone loss, recent clinical trial results have failed to show benefit for other menopausal conditions, such as incontinence.

The long-term benefits and risks of HRT continue to be assessed.

Past perceptions about appropriate indications for the use of HRT were based almost entirely on clinical experience and observational data. These perceptions are being questioned as new knowledge emerges from clinical trials. Some examples follow:

Perception: HRT protects against coronary heart disease.

Evidence: The prospective randomized clinical trials reported so far have not shown benefit for reducing coronary events in secondary prevention.

Perception: Estrogen prevents memory loss and retards the progression of Alzheimer's disease.

Evidence: Clinical trials have not shown that ERT retards progression of early Alzheimer's disease. Clinical trials of the effects of ERT on memory loss are still ongoing.

Perception: Estrogen improves symptoms of depression.

Evidence: Clinical trial data have shown that ERT improves mood and well-being only in women with vasomotor symptoms and sleep disturbance. No convincing clinical trial data indicate that estrogen therapy in postmenopausal women is an effective treatment for major depression.

Perception: Estrogen improves urinary incontinence.

Evidence: Clinical trials have shown no benefit.

Perception: HRT, unlike oral contraceptives, does not increase the risk of venous thromboembolism.

Evidence: Clinical trials confirm a threefold increased risk of venous thromboembolism with oral ERT.

Perception: HRT during the first 5–10 years after the menopause is sufficient to prevent osteoporosis in later life.

Evidence: Bone loss resumes after stopping HRT, leaving women vulnerable to osteoporosis in later life. Whether estrogen is started early or late, it must be continued into old age to maintain skeletal health.

Although many clinically relevant questions remain unanswered, women seeking advice about the menopause now have more information about and more options for healthy postmenopausal years than ever before. New trial results and new medications may further change recommendations for the assessment and management of the postmenopausal woman.

New nonhormone therapies offer more options for prevention of common menopausal conditions, to be tested fully in clinical trials.

We make the following recommendations concerning HRT based on results from clinical trials. Where evidence from clinical trials is not available, we make recommendations based on observational studies. These recommendations are intended as guidelines, not mandates. All interventions should be individualized—tailored to the specific needs and concerns of each woman and designed to provide an optimal quality of life.

2. The Menopause Transition

2.1 Assessment

Some women sail through the menopause transition with no complaints, others are miserable, and the majority have symptoms that are somewhat bothersome. There is still controversy as to which symptoms are related to menopause and which are associated with or exacerbated by other factors.

Clearly not all symptoms that occur during the menopause transition are due to hormonal changes. Only vasomotor, sleep, and some vulvovaginal symptoms have shown more favorable relief after HRT than placebo, and can therefore be convincingly attributed to changing hormone levels and menopause. At least 25 percent of women in clinical trials report significant improvement in their vasomotor symptoms when taking placebo.

Therefore, convincing evidence of treatment benefit requires a placebo-controlled clinical trial.

Women may visit the physician because they have symptoms they suspect are related to menopause or because they want information about the menopause. In either case, assessment for symptoms provides an opportunity to discuss issues that might otherwise remain unaddressed.

Symptoms directly or indirectly related to the menopause transition include:

- Vasomotor symptoms (hot flushes and night sweats)
- Sleep-related symptoms
- Mood changes
- Sexual dysfunction
- Problems with concentration and memory
- Urogenital symptoms

Symptoms can be queried by using a questionnaire or symptom checklist during the interview. Some find that asking about sexual satisfaction is facilitated by the use of a checklist. When a checklist is used, it is important to go beyond the list to assess the severity and duration of reported symptoms and the degree to which they interfere with the woman's life. For example, hot flushes that are not bothersome do not require treatment.

It is important to have a dialogue with the patient. Failure to listen and discuss may explain why many women prescribed HRT do not fill the prescription.

When asking about symptoms, the clinician should be sensitive to each woman's:

- Beliefs and attitudes about menopause, including her medical vs. nonmedical treatment preferences, anxieties, and coping style
- Sociocultural and ethnic background that may affect her concerns and choices
- Work situation, job satisfaction, and stress
- Other life stressors, particularly with personal relationships
- Social supports
- Overall quality of life
- Current use of nonprescription herbal, nutriceutical (a nutritional supplement designed for a specific clinical purpose), or phytoestrogen remedies.

It is important to have a dialogue with the patient. Failure to listen and discuss may explain why many women prescribed HRT do not fill the prescription.

2.2 Symptom Prevention and Treatment. Vasomotor Symptoms: Hot Flushes and Night Sweats

2.2.1 Lifestyle

- Wear layered clothing that can be removed or added as necessary.
- There is conflicting evidence as to whether exercise improves menopause vasomotor symptoms.

2.2.2 Diet

- Avoid hot spicy foods and beverages, and reduce caffeine.
- Avoid alcohol beverages (excess can cause flushing).

2.2.3 Pharmacotherapy

- In a systematic review of more than 40 randomized controlled clinical trials, oral and transdermal estrogen each reduced the severity of vasomotor symptoms, and estrogen was effective in doses lower than the usual 0.625 mg of equine estrogens or equivalent.
- Transdermal estradiol and intranasal 17β-estradiol spray are as effective as oral estrogen in reducing hot flushes.

- Oral tibolone is as effective as other forms of HRT such as estradiol valerate or conjugated estrogens in reducing hot flushes.
- Selective ER modulators can increase hot flushes. In clinical trials, approximately 20 percent of women at least 2 years after menopause less than 60 years of age and 10 percent of older women developed hot flushes on raloxifene. Vasomotor symptoms were mild and rarely led to discontinuation of therapy.
- The selective serotonin reuptake inhibitors (SSRIs) venlafaxine and paroxetine have been shown to substantially reduce hot flushes in clinical trials.
- Progestogens in high daily doses (medroxyprogesterone acetate 20 mg per day or megestrol acetate 40 mg per day) also reduced vasomotor symptoms.
- Veralipride (100 mg per day) reduces hot flushes in patients treated with GnRH agonists.
- Propranolol is no more effective than placebo for the reduction of hot flushes, whereas evidence for clonidine's benefit is inconsistent.

2.2.4 Complementary and Alternative Therapies

- Phytoestrogens have not been shown in most clinical trials to decrease vasomotor symptoms significantly better than placebo. Different results may relate to differences in women (not all of them absorb phytoestrogens equally well) or differences in the products tested. The best single dietary source of phytoestrogens is soy. The U.S. Food and Drug Administration has approved a statement that soy protein at a dose of 25 gm/day may reduce the risk of CVD, based on a modest reduction in total cholesterol level.
- Dong quai has been shown in a clinical trial not to be more effective than placebo for the treatment of hot flushes.
- Evening primrose oil (gamma-linolenic acid) is not more effective than placebo for the reduction of hot flushes.

2.3 Symptom Prevention and Treatment. Urogenital Symptoms

- At least nine RCTs have shown that estrogen improves urogenital symptoms; this is true for oral and transdermal estrogen and for a silicone estradiol-releasing vaginal ring. Vaginal dryness and dyspareunia can be treated with a topical estrogen cream, tablet, or vaginal ring, or with nonhormone moisturizing or lubrication products. In clinical trials, topical estrogen appears to be better than systemic estrogen for relieving these symptoms, and avoids high levels of circulating estrogen.
- In one clinical trial, an estradiol-releasing silicone vaginal ring was also found to reduce the incidence of urinary tract infection.
- Systemic estrogen alone or with a progestin does not reduce incontinence, and in one large clinical trial, HERS, actually increased incontinence.

3. Fractures

3.1 Assessment

When discussing osteoporosis, it is important to be sure that the provider and the patient are using the same language. Some patients confuse osteoporosis (fragile bones) with osteoarthritis (painful joints). Other women (and some doctors) mistakenly believe that a diagnosis of osteoporosis means they should not exercise.

Many factors are associated with an increased fracture risk in women, which may differ by fracture site.

3.1.1 Risk Factors

Many factors are associated with an increased fracture risk in women, which may differ by fracture site. Most available data are on risk factors for spine or hip fractures in Caucasian women aged 65 and older. Predicting risk in younger women and other ethnic groups is less accurate.

Nonmodifiable risk factors for fractures:

- Age—there is an approximate doubling of fracture risk every 7 years
- Family history—history of osteoporotic fracture, especially hip fracture, in either parent or sibling approximately doubles the risk
- Personal history of osteoporotic fracture increases the risk twofold to fivefold
- Early menopause increases risk

Modifiable risk factors:

- Weight—there is an increased risk if thin, and a decreased risk if overweight
- Excessive weight loss is a powerful risk factor for bone loss and fracture
- Current smoking—increases the risk of all fractures
- Low calcium intake—increases the risk of hip fracture
- Vitamin D deficiency—can cause secondary hyperparathyroidism and osteoporosis
- Inadequate physical activity
- Factors associated with falls, some of which are modifiable:
    - Limited vision
    - Impaired cognition
    - Balance problems
    - Alcohol excess
    - Poor health, frailty, muscle weakness
    - Medications, particularly sedatives
    - Environmental hazards, such as poor lighting and loose area rugs
- Low bone density is a risk factor for fracture (fracture risk doubles for every 10–12 percent decrease in bone mineral density, a deviation of approximately—1 t-score or—1 z-score (measured by dual energy x ray absorptiometry [DEXA]).

3.1.2 Case Finding

Bone density testing is recommended in the United States for all women aged 65 years or older.

- DEXA of the hip is currently the gold standard for bone density measurements.
- Bone density results should be used in conjunction with information obtained in clinical risk assessment.

3.2 Prevention and Treatment

Better bones in old age are a function of peak bone mass (usually achieved around age 25), and subsequent rate of bone loss. Peak bone mass is maximized by an adequate calcium intake, physical activity, and not smoking. Lifestyle changes have been shown to improve bone density in young women and to prevent fractures in older women. They are low-cost, safe, and can be recommended widely.

3.2.1 Lifestyle

- Stop smoking
- Avoid extreme weight loss
- Add weight-bearing, muscle-building, and balance exercises
- Avoid sedatives
- Avoid excess alcohol
- Correct visual impairment
- Fallproof the home

3.2.2 Diet

- Correct calcium deficiency. A diet devoid of dairy products rarely provides more than 200 – 250 mg of calcium per day, which does not balance obligatory calcium loss and is associated with increased bone loss. Much of the bone loss can be attenuated by increasing calcium intake. Ideally, the combined diet and supplement intake should be 1,200 mg of calcium each day.
- In correcting dietary calcium deficiency, the first step is to increase calcium-rich foods; each dairy portion contains approximately 300 mg. Calcium-supplemented orange juice or mineral water rich in calcium are useful for women with lactose intolerance.
- If adequate dietary calcium is not likely, calcium supplements should be recommended. Calcium supplementation should be given concomitantly with Vitamin D. Clinical trials have shown that calcium with vitamin D can reduce fracture risk; no clinical trials have shown that vitamin D without calcium significantly reduces fracture risk. Clinical trials consistently show better bone preservation in women who take calcium with estrogen than estrogen alone.
- Supplement vitamin D intake for women 65 and older; 600–800 IU/day together with adequate calcium intake can reduce the risk of fracture in elderly women by about 25 percent.

3.2.3 Pharmacotherapy

With growing evidence for efficacy of osteoporosis treatments and with growing concern about drug costs, policymakers have recommended that expensive drugs not be used for osteoporosis prevention. In addition, all medications have risks and side effects. Therefore, aggressive pharmacotherapy should be reserved for women who are at high risk of fracture in the near future.

Practitioners in discussion with their patients must decide between therapy with bone-specific drugs or broad-spectrum drugs (HRT, SERMs).

- Drugs shown in clinical trials to prevent bone loss, that is, to be effective in prevention of osteoporosis, include estrogen, tibolone, raloxifene, alendronate, and risedronate.
- Drugs shown in clinical trials to prevent fractures include raloxifene, alendronate, and risedronate. These clinical trials were conducted in women at increased risk of fracture. Similar large trials have not been conducted using estrogen or tibolone. HERS found no difference in clinical fracture rate or height loss (a marker for vertebral fractures) in women assigned to HRT vs. placebo. Fracture was a preset secondary endpoint in HERS, but women in this trial were not at high risk for fracture.

Lifestyle changes have been shown to improve bone density in young women and to prevent fractures in older women.

Estrogen therapy

- Bone loss is accelerated during the first 5–10 years following menopause, and postmenopausal estrogen therapy is effective in preserving existing bone, whether begun in old age or at the time of the menopause. Results are similar with estrogen alone or when estrogen is used with a nonandrogenic progestin such as medroxyprogesterone acetate or progesterone. Androgenic progestins such as norethisterone-acetate have a synergistic activity when combined with 17β-estradiol.
- Clinical trials have shown that doses of 0.3 mg per day of conjugated equine estrogen (lower than the previously recommended 0.625 mg per day), 0.5 mg of oral 17β-estradiol, or 25 micrograms of transdermal 17β-estradiol maintain bone in most women when taken with adequate calcium. Smaller doses were better tolerated with regard to fewer episodes of uterine bleeding and less breast tenderness, two major reasons why women discontinue estrogen. Whether

lower dosages of estrogen will be safer (lower rates of venous thomboembolism, breast cancer) remains to be proven.

When medication is indicated, based on a combination of clinical risk factors and low bone mineral density, the choice varies with the age of the patient and the severity of osteoporosis.

- Estrogen must be used continuously to preserve bone. Observational data suggest that bone density in older women who have never received estrogen is similar to bone density in women who used estrogen for 10 years and then discontinued it for another 10 years.
- Hormone treatment of women soon after menopause should be reserved for management of postmenopausal symptoms, but it will preserve bone in most women.

Aggressive pharmacotherapy should be reserved for women who are at high risk of fracture in the near future.

Non-estrogen therapy

Asymptomatic women 10 or more years postmenopause, without severe osteoporosis, may prefer tibolone or raloxifene. For women aged 60 or older who have osteoporosis but are not at high risk for nonspine fracture, raloxifene can be used to reduce the risk of spine fractures and for its possible other health benefits. Older women, particularly those with severe osteoporosis and prior fracture(s), may prefer alendronate or risedronate for their rapid acting bone-specific effects and reductions in nonspine as well as spine fractures.

Parathyroid hormone treatment by daily injection promises to be particularly effective for women with very severe osteoporosis who need to gain substantial amounts of bone.

The way medications are prescribed influences patient adherence. Beginning with a low dose for women prescribed estrogen helps reduce breast pain and slowly increasing dosage of raloxifene is useful in overcoming the hot flush side effect. Women who cannot tolerate the first medication often tolerate one of the other bone-sparing medications. A few trials have shown improved bone density over single therapy when a bisphosphonate is combined with estrogen or raloxifene, but there are no fracture data in women using these combinations (and the cost of combination therapy precludes routine use).

- Statins have been inconsistently associated with higher bone density. Statins have not been consistent in reducing bone loss or fracture risk, and these skeletal benefits have not been assessed in clinical trials.
- Clinical trial data show that a thiazide diuretic reduces but does not prevent bone loss.
- Observational studies suggest that people using thiazides are less likely to have fractures.

3.2.4 Complementary and Alternative Therapies

- Soy food (soy protein isolate) has been shown in clinical trials to have little or no benefit for the skeleton when ingested in the usually recommended amounts (20–25 grams of soy protein per day).
- Ipriflavone, a synthetic isoflavone, has been shown in preliminary studies to reduce bone loss but failed to improve bone density or reduce fracture risk in a large clinical study of women with osteoporosis.

4. Cardiovascular Disease

4.1 Assessment

When assessing a woman's knowledge about heart disease and stroke prevention, it is important to note that cardiovascular disease is a more common cause of morbidity and mortality for women in most of the world than osteoporosis and cancer combined.

4.1.1 Risk Factors

The main risk factors for coronary heart disease are: high blood cholesterol, high blood pressure, diabetes, and cigarette smoking. These same factors also apply to stroke and peripheral arterial disease, but the order of importance differs. High blood pressure is the most important risk factor for stroke, while smoking has been consistently associated with peripheral arterial disease, and high blood cholesterol with CHD.

Nonmodifiable risk factors

- Age. For every 10-year increase in age, the risk for heart disease increases about threefold.
- The presence of CHD or other evidence of atherosclerotic arterial disease including stroke or lower extremity arterial disease increases the risk for myocardial infarction (MI) about fivefold. Atrial fibrillation, aortic stenosis, and narrowing of the coronary arteries are also risk factors for stroke.
- Family history of premature CHD (MI before age 55 in men, 65 in women) increases the risk for MI about twofold.
- The importance of a positive family history is amplified in women who smoke cigarettes.

Modifiable risk factors

- Cigarette smoking: Compared to smokers, nonsmokers or women who stop smoking have one-third the risk for MI.
- Physical activity: Women who walk briskly for 3 hours per week have a one-third lower risk for MI compared to women who do little exercise.
- Nutrition: Women whose usual diet is low in saturated and trans fats, and relatively high in unsaturated fats (including monounsaturated fats and fish oils), and high in cereal fiber, fruits, and vegetables, have half the risk for MI compared to women who do not have this healthy eating pattern.
- Weight: Lean women (body mass index below 25) have one-quarter less risk than overweight women, and less than one-half the risk of obese women (body mass index above 30).
- Fat distribution: Women with a waist circumference of less than 28 inches (71 cm) have one-third the risk for MI compared to women with a waist circumference of more than 38 inches (96.5 cm). Weight and weight distribution associated risks are not the same in all populations. For example, overweight and central obesity seem to be less important risk factors in African American women than in women of northern European ancestry and Asian American women who seem to be at increased risk at lower weights.

CVD is a more common cause of morbidity and mortality for women in most of the world than osteoporosis and cancer combined.

- Psychosocial factors: Life stress situations, depression, and social isolation have been linked to increased risk for MI in women.
- Blood pressure: Women with a systolic blood pressure below 140 mmHg have a risk for MI one-half that of women with a level above 180 mmHg.
- Blood cholesterol: Women with a LDL cholesterol below 130 mg/dL (3.4 mmol/L) have a risk for MI one-half that of women with levels above 190 mg/dL (4.9 mmol/L).
- HDL cholesterol: Women with a HDL cholesterol level above 60 mg/dL (1.6 mmol/L) have a risk for MI which is one-third that of women with a level of less than 40 mg/dL (1.0 mmol/L). Contrary to popular opinion, women with high HDL cholesterol levels are not immune to MI.
- Triglycerides: Women with triglyceride levels below 150 mg/dL (1.7 mmol/L) have a risk of MI one-third lower than women with levels above 240 mg/dL (2.7 mmol/L).

- Diabetes: Women with diabetes by history or glycemia (fasting plasma glucose > 126 mg/dL (7.0 mmol/L) and/or 2 hour postchallenge glucose above 199 mg/dL (11.1 mmol/L) have a two- to fourfold increased risk of MI compared to women without diabetes. About half of women with Type 2 diabetes do not know they have it. Diabetes is often first diagnosed when the patient has a MI.

4.1.2 Other Assessments

History

- Presence of any of the risk factors above.
- Symptoms compatible with transient ischemic attack, CHD, or lower extremity atherosclerosis.
- Use of HRT, antihypertensive drugs, lipid-lowering therapy, aspirin, and medication for diabetes.

Physical examination

- Pulses, auscultation for cardiac murmurs, and arterial bruits.
- Blood pressure at first visit. Women who have optimal blood pressure levels (< 130/85 mmHg) are rechecked every 2 years (Europe: women > 40 years: every year), those with normal levels (< 140/90 mmHg) are rechecked every year. Women with levels > 140/90 mmHg need confirmation.
- Height, weight, waist circumference, calculate body mass index.

The main risk factors for CHD are: high blood cholesterol, high blood pressure, diabetes, and cigarette smoking.

Laboratory tests

- Fasting glucose, total cholesterol, HDL cholesterol, triglycerides, calculated LDL cholesterol at first visit. For women without known CHD, the desirable lipid levels are LDL cholesterol < 130 mg/dL (3.4 mmol/L), triglycerides < 150 mg/dL (1.7 mmol/L), and HDL cholesterol levels > 45 mg/dL (1.3 mmol/L).
- Repeat measurements that are normal every 5 years.
- Evidence does not support further screening for diabetes. Case finding may be appropriate in persons who have central obesity, high triglycerides, or a positive family history. Repeat glucose tests for women whose fasting blood glucose is elevated because the diagnosis of diabetes needs a confirmatory test. Women whose fasting plasma glucose is between 110 (6.1 mmol/L) and 126 mg/dL (7.0 mmol/L) or whose 2 hour glucose is between 140 (7.8 mmol/L) and 200 mg/dL (11.1 mmol/L) are at high risk of future diabetes.
- In some countries, homocysteine measurement is recommended.

Other tests for CHD, cerebral arterial disease, and peripheral vascular disease as indicated by symptoms. The combined effect of two or more risk factors is more powerful than any single risk factor, and some risk factors commonly occur together. (For example, screening for diabetes may be most appropriate in persons with high blood pressure or high triglyceride levels.) When one risk factor is found, the presence of other factors should be sought and an assessment of overall risk should be made by counting the number of risk factors plus a 10-year risk assessment as in the National Cholesterol Education Program's Adult Treatment Panel III Report (NCEP ATP III) or as an assessment of the 10-year risk as recommended in European guidelines. Risk assessment can be used to motivate the patient to make lifestyle changes and comply with medication.

4.2 Prevention and Treatment

Even in the absence of clinical trial data, lifestyle and diet recommendations can be made to all women, not just those with heart disease risk factors or disease, because the diet, physical activity, and not smoking recommendations represent a return toward the evolutionary norm.

4.2.1 Lifestyle

- At each visit, reinforce nonsmoking status, or strongly encourage patient (and family) to stop smoking and avoid secondhand smoke. Prescribe counseling, nicotine replacement, or other pharmacotherapy as indicated in conjunction with behavioral therapy or a formal smoking cessation program.
- Encourage a minimum of 30 minutes of moderate-intensity dynamic exercise, e.g., brisk walking, at least 3 days a week, supplemented by an increase in daily lifestyle activities. Women who want to do more than the minimum should be encouraged to do so. Recommend medically supervised programs for women who have had a recent MI or revascularization procedure.

Women with diabetes … have a two- to fourfold increased risk of MI …

- Encourage gradual weight loss for overweight women through a combination of physical activity and portion control, healthy food choices, and recognition of triggers to overeating. Refer to weight loss support group or formal nutritional counseling when appropriate.
- Encourage positive coping mechanisms for stress (e.g., substitute physical activity for overeating or smoking in response to stressful life situations).

4.2.2 Diet

- Encourage a well-balanced and diversified eating pattern that is low in saturated fat and high in fresh fruits and vegetables and fiber. Prefer fats with higher monounsaturated content (e.g., olive oil, canola oil). Prefer seafood and skinless chicken to red meat. Prefer soft unsaturated margarine to hard margarine or butter. Use skim milk and skim milk products or at most 1 percent milk instead of products with a higher fat content. Limit the intake of high-cholesterol foods, avoid fast-food meals. Consume more than five servings of fruits and vegetables daily. Total dietary fiber intake from food should be 25–30 g per day.
- A clinical trial showed that eating fish two to three times per week reduced the risk of CVD.
- Encourage increased dietary consumption of omega-3 fatty acids.
- A clinical trial showed that a "Mediterranean diet," supplemented with alpha-linoleic acid, significantly reduced the risk of recurrent coronary events in patients with heart disease.
- Diets rich in antioxidant vitamins (i.e., nuts, fruits, and vegetables) are preferred over vitamin supplements.
- Limit salt intake to 6 g per day. A reduced salt/reduced saturated fat diet has been shown to reduce blood pressure in clinical trials.
- Prefer spices to salt in food preparation. Reduce intake of canned and commercial bakery goods, which are usually high in salt.
- Limit alcohol to less than one to two glasses per day: one glass equals 4 ounces of wine (approx. 120 mL), 12 ounces of beer (approx. 360 mL), or 1½ ounces of 80-proof spirits (approx. 45 mL).

4.2.3 Pharmacotherapy

Blood pressure

- Achieve and maintain blood pressure < 140/90 mmHg or lower if tolerated. If blood pressure remains above 140/90 mmHg after 3 months of reduced dietary salt, saturated fats and attempted weight loss, or if initial level is above 160/100 mmHg, initiate individualized pharmacotherapy. Goal blood pressure < 130/80 mmHg if diabetic.

  Beta-blockers, low-dose diuretics, and angiotensin converting enzyme inhibitors have been shown in clinical trials to reduce the risk of MI in patients with high blood pressure.

Lipids and lipoproteins

- **LDL cholesterol**

  a) In women without CHD or CHD risk equivalents (other forms of atherosclerotic disease, diabetes, or 10-year risk more than 20 percent), the desirable LDL cholesterol level is < 130 mg/dL (3.4 mmol/L).

     ◦ If the LDL cholesterol level is > 130 mg/dL (3.4 mmol/L) and two or more other risk factors are present, or the 10-year risk of MI is more than 10 percent, implement intensive lifestyle intervention and consider pharmacotherapy. If the 10-year risk is less than 10 percent, consider pharmacotherapy if the LDL cholesterol is > 160 mg/dL (4.1 mmol/L).

     ◦ If the LDL cholesterol level is > 190 mg/dL (4.9 mmol/L), pharmacotherapy is usually required.

  b) In women with CHD or CHD equivalents, the desirable LDL cholesterol level is 100 mg/dL (2.6 mmol/L) or lower, and pharmacotherapy is generally required.

- **Triglycerides and HDL cholesterol**

  ◦ If the triglycerides are >150 mg/dL (1.7 mmol/L) and the HDL cholesterol is below 40 mg/dL (1.0 mmol/L), treatment should still be aimed primarily at the LDL level. Lowering triglycerides and raising HDL levels become secondary targets of therapy and may influence the choice of drugs. Women with elevated triglycerides as their only lipid abnormality usually respond to intensive lifestyle measures. Some patients with very high triglyceride levels respond best to fibrates or niacin.

Even in the absence of clinical trial data, lifestyle and diet recommendations can be made to all women …

- **Choice of drugs**

  ◦ Statins are the drugs of choice for high LDL cholesterol levels, irrespective of the levels of triglycerides or HDL cholesterol. Statins have been shown in clinical trials to reduce the risk of MI and stroke.

  For women with moderate elevations of LDL cholesterol, raised triglycerides, and low HDL cholesterol levels, statins are the first choice. Fibrates and niacin have not been shown in randomized clinical trials to reduce CHD risk in women, although recommended in AHA/ACC (American Heart Association/ American College of Cardiology) guidelines for low HDL or high triglycerides. Start statin therapy promptly in patients with acute coronary syndrome.

  HRT given orally reduces LDL cholesterol by 10 percent, raises HDL cholesterol by 10 percent, and raises triglycerides by 20 percent. HRT is not recommended for management of lipid disorders because of the lack of clinical trial evidence showing cardiovascular benefit.

Diabetes

- Target preprandial blood glucose in the range of 80–120 mg/dL (4.4–6.7 mmol/L), bedtime 100–140 mg/dL (5.5–7.8 mmol/L), Hgb A1c < 7 percent
- Maintain LDL cholesterol < 100 mg/dL (2.6 mmol/L) and triglycerides < 150 mg/dL (1.7 mmol/L)
- Maintain blood pressure < 130/80 mmHg (optimal < 120/75 mmHg)
- In clinical trials, the initiation of oral HRT is accompanied by a two- to fourfold increased risk of venous thromboembolism and a small early increased risk of CHD and stroke. Based on observational studies, a reduction in risk for CHD after 2 or more years is possible, but the clinical trial evidence is lacking. Some experts

see no reason to discontinue HRT in women who have been treated for many years, in view of the expected benefit for osteoporosis. Based on clinical trial data, an increased risk of venous thromboembolic disease persists for at least 4 years. The absolute increase in risk for venous thromboembolism is small—approximately two excess events in 8,000 treated women. This risk may be reduced in women taking aspirin or statins.

- A history of venous thromboembolic disease is a contraindication to HRT.
- Low-dose aspirin can be recommended for women with established CVD (based on clinical trial data and probably for high-risk women [by inference only]). There is some concern that the risk benefit ratio may be different in women, who seem to have a higher risk of stroke than men. Consider clopidogrel or warfarin if aspirin is contraindicated.
- Beta-blockers: If there are no contraindications (e.g., severe bradycardia, high degree heart block, acute heart failure, asthma, active peripheral vascular disease) start beta-blockers within hours of hospitalization for MI and acute coronary syndromes, or as soon as possible thereafter to lower the risk of reinfarction and of cardiac failure.
- ACE inhibitors. If there are no contraindications (e.g., renal artery stenosis, aortic stenosis, or severe hypotension), start ACE inhibitors within hours of hospitalization for MI, or as soon as possible thereafter, to lower the risk of reinfarction and of cardiac failure. Use ACE inhibitors to lower the risk of MI and death in patients with cardiac failure, left ventricular dysfunction, or high risk for CHD.

4.2.4 Complementary and Alternative Therapies

- Trials of vitamin E and beta-carotene supplements have failed to show benefit for CVD prevention.

5. Cancers (breast, cervix, colorectal, endometrial, ovary, and lung)

The major cancers that occur in postmenopausal women are breast, cervix, colorectal, endometrial, ovary, and lung.

In observational studies, the increased risk of breast cancer after 5 or more years of estrogen replacement therapy is similar to the risk associated with a delayed menopause or with obesity. In some of these studies, breast cancer risk was higher in women who used estrogen plus a progestin and higher in women who used estrogen plus progestin cyclically.

Endometrial cancer is associated with endogenous or unopposed exogenous estrogen levels. An increased risk of endometrial cancer occurs in menopausal women who have low levels of progestin to counterbalance the stimulating effect of estrogen on the endometrium. A 3-year clinical trial has shown that endometrial hyperplasia, a uterine cancer precursor, occurs in 10 percent of women for each year of unopposed estrogen use.

A number of observational epidemiological studies (including both prospective and case-control studies) have consistently shown that women on HRT have reduced risks of developing colorectal cancer or adenoma and of dying from colorectal cancer. There is weak evidence from observational studies that HRT increases the risk of ovarian and lung cancer.

Much of the increased risk for cancers in postmenopausal women can be linked to the effects of age and accumulated lifetime exposure to carcinogens.

5.1 Assessment

5.1.1 Risk Factors

Nonmodifiable risk factors

- Family history of breast, ovarian, or colorectal cancer, especially in a first-degree relative.
- Age. Most cancer rates increase with age. The year-by-year increase in breast cancer rates

persists but is less steep in women who do not take estrogen after the menopause.

- Previous history of cancer (invasive and in situ).
- Precursor lesions (benign proliferative breast disease, colorectal polyps, endometrial hyperplasia, and high grade squamous intra-epithelial lesions of the cervix infected with selected variants of human papillomavirus [HPV]).
- Reproductive and menstrual factors: Early menarche and late menopause increase risk for breast cancer, and possibly also endometrial and ovarian cancer. Early first pregnancy and multiparity decrease the risk for breast and ovarian cancers. Multiparity also reduces the risk of endometrial cancer.

In observational studies, the increased risk of breast cancer after 5 or more years of estrogen replacement therapy is similar to the risk associated with a delayed menopause or with obesity.

Modifiable risk factors

- Estrogen treatment: Excess exogenous estrogen in the postmenopausal years increases risk for breast and endometrial cancers. It is unknown whether lower doses of estrogen will have different risks and benefits. Use of a progestin with the estrogen may increase breast cancer risk, but it decreases endometrial cancer risk if taken in an adequate regimen, either 10–14 days per month or daily. Past oral contraceptive use greater than 1 year decreases endometrial and ovarian cancer risk.
- Overweight: Heavier postmenopausal women are at increased risk for cancer of the breast, endometrium, and colon. The risk for breast cancer in obese women is comparable to that for long-term HRT.
- Nutrition: Women whose usual diet is low in fat and high in vegetables, fruits, and fiber have a reduced risk for colorectal and breast cancer. Recent clinical trials found no reduced risk of colon polyps, a cancer precursor, after either a high-fiber diet or a diet enriched with fruits and vegetables.
- Physical activity: Physically active women may have a reduced risk for colon cancer and possibly also breast and endometrial cancer.
- Cigarette smoking: Women smokers are at increased risk for lung, cervix, colorectal, oral, esophageal, and pancreatic cancers, as well as other less common epithelial cell cancers.
- Alcohol: Alcohol use increases the risk for breast (probably by increasing endogenous estrogen levels) and colon cancer, as well as more rare head and neck cancers.
- Radiation: High doses of radiation, used in the past for certain medical treatments, have been associated with increased risk for several cancers.
- Other exposures: Women infected with specific strains of HPV are at increased risk for cervical cancer.
- High radiographic density on mammogram carries about a twofold increased risk for breast cancer and may delay diagnosis by making mammograms harder to read. A clinical trial showed that this reversible condition occurs within 1 year in about 15 percent of most postmenopausal women treated with estrogen alone and in more than one-third of those treated with estrogen plus a progestin.

5.1.2 Case Finding

History

- Presence of any of the risk factors above

Physical examination

- Height, weight
- Clinical breast exam

- Pelvic exam
- Colorectal screening (can include fecal occult blood assay, flexible sigmoidoscopy, and colonoscopy).

Specific tests

The selection of screening modality and frequency will depend on individual and population prevalence of disease and available resources.[a]

- Mammograms: There is disagreement about the benefit of mammograms before age 50, but women taking HRT and those with other risk factors may want to be tested. Mammograms are usually performed annually or biannually. Because women's risk of breast cancer continues to increase with age, regular mammography screening remains appropriate even in old age although the benefit in women over age 75 has not been tested.
- Cervical smears: In countries where cervical cancer rates increase with age, cervical smears should be continued into old age.
- Pap smears have poor positive predictive value for postmenopausal women and do not have to be performed more often than every 2–3 years after a normal cytological result. The main advantage of an annual Pap smear is that it increases overall adherence to regular examination. Clinical observation shows no effect of HRT on cytologic abnormalities.
- Special methods that include testing for carcinogenic HPV strains reduce the number of false-positive results and the attendant anxiety and cost. In the future, these tests may replace the Pap smear as the gold standard for early detection of cervical cancer.

5.2 Prevention and Treatment

Despite a great deal of information on factors that increase cancer risk, there are limited data on what can be done to reduce risk. There have been few clinical trials of prevention modalities. It is not clear that reversing a risk factor will reduce cancer risk. Nevertheless, some practical recommendations can be made.

Much of the increased risk for cancers in postmenopausal women can be linked to the effects of age and accumulated lifetime exposure to carcinogens.

5.2.1 Lifestyle

- Stop smoking.
- Limit alcohol use to less than one to two glasses per day: 1 glass equals 4 ounces of wine (approx. 120 mL), 12 ounces of beer (approx. 360 mL), or 1½ ounces of 80-proof spirits (approx. 45 mL).
- Avoid unnecessary radiation.
- Avoid unopposed ERT if uterus is present.
- Avoid HRT for more than 5 years except in presence of specific indications.
- Avoid postmenopausal weight gain.
- If overweight or obese, lose weight.
- Increase physical activity.

5.2.2 Diet

- Increase intake of vegetables, fruits, and fiber.
- Decrease fat and red meat intake.

[a] Horton R. Screening mammography—an overview revisited. Lancet 2001;358:1284–1285. Olsen O, Gotzsche PC. Cochrane review on screening for breast cancer with mammography. *Lancet* 2001;358:1340–1342.

5.2.3 Pharmacotherapy

Breast Cancer

- Consider tamoxifen use if high risk for breast cancer; a North American clinical trial found a reduced risk for breast cancer with 5-year use. Tamoxifen increases the risk of endometrial cancer, venous thromboembolism, and vasomotor symptoms.

Despite much interest in complementary and alternative therapies, there are no trial data on their efficacy in reducing cancer risk.

- Although raloxifene is not approved for prevention or treatment of breast cancer, a 4-year trial of raloxifene in women with osteoporosis (not at high risk for breast cancer) showed a 90-percent risk reduction for estrogen-receptor positive breast cancer, and no increased risk of uterine cancer. Breast density is not increased with raloxifene use. A trial comparing raloxifene with tamoxifen is underway.
- When prescribing estrogen to women with an intact uterus, prescribe at least 10–14 days per month of progestin, to reduce endometrial cancer risk.
- Do not give progestin to women without a uterus; it is not necessary, and some observational studies suggest that estrogen plus progestin increases the risk of breast cancer more than estrogen alone.

5.2.4 Complementary and Alternative Therapies

- Despite much interest in complementary and alternative therapies, there are no trial data on their efficacy in reducing cancer risk. The most attractive candidate is soy protein, based on observational studies of low breast cancer risk in countries with high soy intake.
- A trial of the effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas, a cancer precursor, failed to show the benefit of such a diet in reducing risk.

Other: very-high-risk patients

- Consider removal of at-risk organs.
- Very high risk for breast cancer: additional screening by sonography.
- There is no trial evidence that additional screening such as pelvic ultrasound or Ca125 for women at high risk for ovarian cancer or beginning mammography before age 40 for women at high risk for breast cancer will improve the prognosis.
- Colonoscopy for women at high risk for colorectal cancer can be recommended based on clinical trial data.

6. Dementia and Mental Health

For most disorders affecting the central nervous system, there are inadequate data upon which to base practice decisions. Alzheimer's disease merits particular mention, because it is common and a major concern of older women.

6.1 Assessment

6.1.1 Risk Factors for Alzheimer's Disease

- The only consistently identified risk factors are age, family history, and apolipoprotein E ε4 allele.
- The risk of developing Alzheimer's disease doubles approximately every 5 years through the ninth decade of life.
- Uncommon forms of the illness that appear before the seventh decade of life are often transmitted as autosomal dominant disorders.
- Dominant inheritance is not characteristic of later-onset dementia, although family history remains a risk factor in this age group.
- Some observational studies suggest other risk factors for Alzheimer's disease, including prior history of head trauma, low educational achievement, presence of CHD, hypertension or hyperlipidemia, prior history of depression, and the

absence of HRT. The evidence for these associations is inconsistent.

- Polypharmacy and thyroid disease are two examples of reversible causes of memory loss in older adults.
- Depressed mood is fairly common in persons with dementia; it may impair cognitive function or be a consequence of it.

6.1.2 Case Finding for Suspected Dementia

- The medical, neurological, and psychiatric history should focus on potential causes of cognitive and behavioral change, including stroke, endocrine disease (e.g., thyroid disorders), toxic exposures (particularly the excessive use of psychotropic medications or medications with psychotropic side-effects), and depression.

For most disorders affecting the central nervous system, there are inadequate data upon which to base practice decisions.

- Family history should be assessed.
- Functional decline should be documented.
- The mental status examination should evaluate both cognition and mood. Commonly used tests for cognitive function are the Mini-Mental State Examination (MMSE) and the short Blessed Test for Orientation-Memory-Concentration. Standard validated questionnaires are available for testing for depressed mood in the elderly (e.g., the Beck Depression Inventory and the Geriatric Depression Scale).
- Laboratory assessment in the patient with dementia usually includes complete blood count; serum electrolytes and glucose; tests of renal, liver, and thyroid function; and B-12 level. Screening for syphilis and HIV should be considered in at-risk populations.
- Brain imaging study (CT scan or MRI scan) is often used to exclude space-occupying lesions, evaluate suspected cerebrovascular disease, or evaluate suspected hydrocephalus. The diagnostic yield for this procedure is low if the neurological examination is normal and the history and examination are otherwise typical for Alzheimer's disease.
- A common cause of cognitive impairment in the elderly is overmedication. A careful review of all medications taken by the patient may lead to the identification of a reversible cause of confusion or memory loss.

6.2 Prevention and Treatment

- There are no proven preventive measures for Alzheimer's disease. For prevention of vascular dementia, it is reasonable to follow preventive recommendations listed for CVD.

6.2.1 Lifestyle

- Ensure a safe, stable, and structured environment.
- Encourage social interventions such as power of attorney and caregiver respite as appropriate.

6.2.2 Diet

- Diet should be well-balanced.
- Discourage excess alcohol use.
- Discourage smoking, which can pose a fire hazard.

6.2.3 Pharmacotherapy

- Reduce unnecessary or optional medications.
- Identify and treat depression and other behavioral disturbances when they are distressing to patients or hinder their care.
- There is clinical trial evidence that drugs that inhibit the breakdown of acetylcholine in the brain are often of mild symptomatic benefit.

- There is no clinical trial evidence that estrogen improves symptoms or delays symptomatic progression in women with Alzheimer's disease.
- There are no published long-term clinical trial data on potential effects of HRT on age-associated cognitive decline.
- One clinical trial found that vitamin E slows progression without improving cognition in patients with moderate dementia due to Alzheimer's Disease.
- One clinical trial of antihypertensive medication in cognitively intact older adults with hypertension showed a small but significant difference in the rate of memory loss and the incidence of dementia in those on active treatment.
- One clinical trial found raloxifene was associated with less cognitive decline in two cognitive function tests in older women.

6.2.4 Complementary and Alternative Therapies

- There is limited trial evidence that gingko biloba may offer mild cognitive benefit when given to patients with dementia.

7. Conclusions

In the last 20 years, menopause has become a household word, with much better understanding of its consequences. The growing numbers of postmenopausal women and clinical trials have coincided to draw increasing attention to the perimenopausal and postmenopausal years. Better studies of older therapies and the expanded number of new choices today, with more in development and evaluation, have complicated provider and patient choices, but greatly improved the potential for effective intervention.

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14. List of Abbreviations

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACS	acute coronary syndromes
ACTH	adrenocorticotropic hormone
AF–1	activation function 1
AF–2	activation function 2
AHA	American Heart Association
AHCPR	Agency for Health Care Policy and Research
AHRQ	Agency for Healthcare Research and Quality
AIRE	Acute Infarction Ramipril Efficacy
AP1	Activated Protein 1
AR	androgen receptor
ArKO	aromatase knockout
ATP	Adult Treatment Panel
AVP	anteroventral periventricular nucleus
BARI	Bypass Angioplasty Revascularization Investigation
BCDDP	Breast Cancer Detection and Demonstration Project
BERKO	ERβ knockout
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
CABG	coronary artery bypass graph
CAD	coronary artery disease
CAMS	Council of Affiliated Menopause Societies
CAST	Chinese Acute Stroke Trial
CBP	CREB binding protein
CEE	conjugated equine estrogen
ChAT	choline acetyl transferase
CHD	coronary heart disease
CI	confidence interval
CNS	central nervous system
CONSENSUS-I	Cooperative North Scandinavian Enalapril Survival Study
CPS-II	Cancer Prevention Study II

CRP	C-reactive protein
CT	computed tomography
CVD	cardiovascular disease
D&C	dilatation and curettage
DDT	dichlorodiphenyltrichloroethane
DERKO	double ER knockout
DES	diethylstilbestrol
DEXA	dual energy x-ray absorptiometry
DRI	dietary reference intake
DSM IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
ECG	electrocardiogram
EGF	epidermal growth factor
eNOS	endothelial nitric oxide synthase
EPISTENT	Evaluation of IIb/IIIa Platelet Inhibitor for Stenting
EpRE/ARE	electrophilic/antioxidant response element
ER	estrogen receptor
ERA	Estrogen Replacement and Atherosclerosis
ERE	estrogen-responsive element
ERKO	ERα knockout
ERT	estrogen replacement therapy
FARs	floating absolute risks
FDA	Food and Drug Administration
FMP	final menstrual period
FSH	follicle-stimulating hormone
GABA	gamma-aminobutyric acid
GBDS	Global Burden of Disease Study
GH	growth hormone
GnRH	gonadotropin-releasing hormone
GUSTO IIb	Global Use of Strategies To Open Occluded Coronary Arteries in Acute Coronary Syndromes
HATs	histone acetyl transferases
HDL	high density lipoprotein
HERS	Heart and Estrogen/Progestin Replacement Study
hGH	human growth hormone
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HOPE	Heart Outcomes Prevention Evaluation
HPA	hypothalamo-pituitary axis
HPV	human papillomavirus
HRT	hormone replacement therapy
HSDD	hypoactive sexual desire disorder
5-HT	5-hydroxytryptamine
ICAM-1	intracellular adhesion unit
ICD-10	International Statistical Classification of Diseases and Related Health Problems

ICI	Imperial Chemical Industries PLC
IGF-I	insulin-like growth factor
IL-1b	interleukin-1b
IMS	International Menopause Society
ISIS	International Studies of Infarct Survival
IU	international unit
IUD	intrauterine contraceptive device
LBD	ligand-binding domain
LDL	low density lipoprotein
LH	luteinizing hormone
Lp(a)	lipoprotein(a)
LV	left ventricular
MAPK	mitogen-activated protein kinase
MEK	mitogen-activated protein kinase kinase
MI	myocardial infarction
MMP	matrix metalloproteinases
MMSE	Mini-Mental State Examination
MORE	Multiple Outcomes of Raloxifene Evaluation
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
NCEP	National Cholesterol Education Program
NGF	nerve growth factor
NHANES III	Third National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NO	nitric oxide
NRMI	National Registry of Myocardial Infarction
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSAIDs	nonsteroidal anti-inflammatory drugs
OAB	overactive bladder
OC	oral contraceptive
OR	odds ratio
ORWH	Office of Research on Women’s Health
PAI	plasminogen activator inhibitor
PAMI	Primary Angioplasty in Myocardial Infarction
PEPI	Postmenopause Estrogen/Progestin Intervention
PIN	prostatic intraepithelial neoplasia
PKA	protein kinase A
PKC	protein kinase C
PPARs	peroxisome proliferator-activated receptors
PR	progesterone receptor
PRL	prolactin

PTCA	percutaneous transluminal coronary angioplasty
PTH	parathyroid hormone
RCT	randomized controlled trial
RR	relative risk
RU486	mifepristone
RUTH	Raloxifene Use for The Heart
SAD	sexual aversion disorder
SERM	selective estrogen receptor modulator
SERT	serotonin reuptake transporter
SHBG	sex hormone binding globulin
SHEP	Systolic Hypertension in the Elderly Program
SSRI	selective serotonin reuptake inhibitors
STAR	Study of Tamoxifen and Raloxifene
STOP	Swedish Trial in Old Patients
STS	Society of Thoracic Surgeons
SWAN	Study of Women's Health Across the Nation
TGF	transforming growth factor
THC	tetrahydrochrysene
TNFa	tumor necrosis factor a
TPH	tryptophan hydroxylase
TTS	transdermal therapeutic systems
UI	urinary incontinence
VCAM-1	vascular cell adhesion molecule-1
W/H	waist/hip ratio
WHI	Women's Health Initiative
WHO	World Health Organization
WISDOM	Women's International Study of Long Duration Oestrogen After Menopause

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NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Phone: 301-592-8573
Fax: 301-592-8563
TTY: 240-629-3255
Web: *http://www.nhlbi.nih.gov*